REMARKS/ARGUMENTS

Claims 30, 32-35, 37-47, and 49-69 are currently pending and under examination in the application.

Claims 1-29, 31, 36, and 48 have been cancelled, and claims 30, 32, 37, 39, 40, 46, 47, 49, and 53 have been amended, without prejudice or disclaimer, solely for the purpose of expediting patent prosecution in accordance with the U.S. Patent Office Business Goals (65 Fed. Reg. 54604 (September 8, 2000)).

Claims 63-69 have been newly added to more fully encompass Applicants' invention.

Amended claim 30 recites "orally administered," "a total daily dose of up to about 600 mg," and "administration of SAHA," and transposes recitation of "or a pharmaceutically acceptable salt or hydrate thereof" (see, *inter alia*, page 7, lines 1-10; page 10, lines 20-21; page 11, lines 8-11; page 57, lines 8-11 and lines 29-31; page 58, lines 1-3 of the application as originally filed).

Amended claims 37, 49, and 53 have been corrected to contain proper dependencies.

Amended claim 39 recites "twice daily at a dose of about 150 mg, 200 mg, or 300 mg" (see, *inter alia*, page 57, lines 12-22 of the application as originally filed).

Amended claim 40 recites "twice daily at a dose of about 150 mg, 200 mg, or 300 mg intermittently" (see, *inter alia*, page 57, lines 18-28 and page 59, lines 6-11, 15-23 of the application as originally filed).

Amended claim 46 recites "three times daily at a dose of about 100 mg or 150 mg" (see, *inter alia*, page 57, lines 15-22 of the application as originally filed).

Amended claim 47 recites "orally administered" and "administration of SAHA,"

and transposes recitation of "or a pharmaceutically acceptable salt or hydrate thereof" (see, *inter alia*, page 7, lines 1-10; page 11, lines 8-11; page 57, lines 5-11 of the application as originally filed).

New claim 63 recites "wherein said composition is administered at a dose of 400 mg continuously" (see, *inter alia*, page 57, lines 20-21, 29-31; and page 58, lines 4-5 of the application as originally filed).

New claim 64 recites "wherein said composition is administered at a dose of 600 mg continuously" (see, *inter alia*, page 57, lines 8-11, 29-31; and page 58, lines 12-14 of the application as originally filed).

New claim 65 recites "wherein said composition is administered at a dose of 400 mg intermittently" (see, *inter alia*, page 57, lines 20-21, 23-28; and page 58, lines 6-11 of the application as originally filed).

New claim 66 recites "wherein said composition is administered at a dose of 600 mg intermittently" (see, *inter alia*, page 57, lines 8-11, 23-28; and page 58, lines 15-23 of the application as originally filed).

New claim 67 recites "wherein said composition is administered at a dose of 400 mg for 14 consecutive days in a 21 day schedule" (see, *inter alia*, page 57, lines 20-21; page 58, lines 28-30 of the application as originally filed).

New claim 68 recites "wherein said composition is administered at a dose of 600 mg for 14 consecutive days in a 21 day schedule" (see, *inter alia*, page 57, lines 8-11; and page 58, lines 28-30 of the application as originally filed).

New claim 69 recites "wherein SAHA is administered" (see, *inter alia*, page 15, lines 2-6 of the application as originally filed).

These amendments are supported by the application as originally filed, and do not constitute new matter. Support for the amendments is shown in parentheses, above. Entry of these amendments is respectfully requested.

Information Disclosure Statement

The Information Disclosure Statements filed March 14, 2005, September 13, 2005, and June 9, 2005 have been considered by the Examiner. The Information Disclosure Statement filed April 6, 2004 has not been considered by the Examiner (Office Action, page 2). The Examiner states that copies of the references for the Information Disclosure Statement were not submitted to the Patent Office. *Id.*

Applicants respectfully note that copies of references in an Information Disclosure Statement are not required where the information was previously cited by or submitted to the Office in a prior application and this prior application is clearly identified in the Information Disclosure Statement and relied on for an earlier filing date under 35 U.S.C. §120. *See* MPEP §609(III)(A)(2). It is further noted that copies of U.S. patents and published applications are not required for all applications filed after June 30, 2003. *Id.*

In the instant case, the Information Disclosure Statement filed April 6, 2004 indicated in bold text that the listed references were previously filed with prior application 10/379,149 filed March 4, 2003 (Exhibit 1, page 3, bottom; see, also, page 1, lines 5-10 of the instant application). This is confirmed by the Information Disclosure Statement filed February 26, 2004 for prior application 10/379,149 (Exhibit 2, pages 1-3). In addition, the filing date of the instant application is noted as September 16, 2003, which falls after the designated date of June 30, 2003. *See* MPEP §609(III)(A)(2).

Reconsideration of the cited references is respectfully requested.

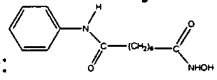
35 U.S.C. §102(a) and (b)

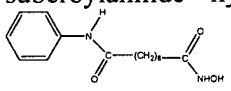
Claims 1, 2, 30, and 47 have been rejected under 35 U.S.C. §102(a) or (b) as allegedly being anticipated by O'Connor et al., 2001, *J. Amer. Soc. Hematol.* 611a,

Abstract No. 2562 ("O'Connor"; Office Action, page 2). The Examiner states that O'Connor reports use of 600-900 mg/m^2 SAHA, "i.e., up to about 800 mg" to obtain stabilization of large cell lymphoma, thereby anticipating the instant claims. *Id.* Applicants respectfully traverse this rejection.

Under 35 U.S.C. §102, a claim is anticipated only if each and every element set forth in the claim is found in the cited reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); MPEP §2131. The invention must be taught by the cited reference in complete detail, as presented in the claims. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989); MPEP §2131.

Applicants note that claims 1 and 2 have been cancelled without prejudice or disclaimer as a result of this Amendment (see above). In addition, claims 30 and 47 currently read:

> 30. A method of treating diffuse large B-cell lymphoma in a subject, said method comprising the step of *orally administering* to the subject a total daily dose of *up to about 600 mg* of a pharmaceutical composition comprising suberoylanilide hydroxamic acid (SAHA) represented by the structure:  or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or diluent, wherein administration of SAHA is effective to treat diffuse large B-cell lymphoma in said subject. (Emphasis added).

> 47. A method of treating diffuse large B-cell lymphoma in a subject, said method comprising the step of *orally administering* to the subject a total daily dose of *up to about 800 mg* of a pharmaceutical composition comprising suberoylanilide hydroxamic acid (SAHA) represented by the structure:  or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or diluent, wherein the amount of SAHA is effective to treat diffuse large B-cell lymphoma in said subject. (Emphasis added).

As such, all of the current claims encompass methods of treatment by orally administering to the subject a total daily dose of up to about 600 mg, or up to about 800

mg, of a pharmaceutical composition comprising suberoylanilide hydroxamic acid (SAHA).

Yet, O'Connor reports only *intravenous administration* of SAHA and does not teach or suggest oral delivery (see abstract). Further, for clarification, it is noted that O'Connor reports intravenous delivery of SAHA to patients with Non-Hodgkin's Lymphoma and Hodgkin's disease. No patients with diffuse large B-cell lymphoma are mentioned (see abstract). Moreover, it is noted that mg/m^2 and *mg* are not the same (see, *e.g.*, Baker *et al.*, 2002, *J. Natl. Canc. Inst.* 94:1883-1888; Exhibit 3, page 1883, right column). It is further noted that intravenous dosages (*e.g.*, mg/m^2 values) can greatly differ from oral dosages (*e.g.*, mg values) due to low bioavailability of oral formulations (see, *e.g.*, abstract from Schellens reference, Exhibit 5, discussed below).

Thus, O'Connor does not teach or suggest all of the aspects of the instant claims, and cannot anticipate the present invention. Reconsideration is respectfully requested.

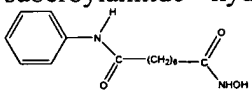
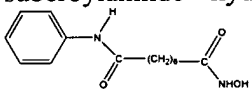
35 U.S.C. §103(a)

Claims 1-3 and 7-62 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over DiMartino, U.S. Patent No. 6,905,669 ("DiMartino"; Office Action, pages 3-4). Claims 4-6 have also been rejected as allegedly unpatentable over DiMartino in view of WO 98/55449 and WO 95/31977. The Examiner states that it would have been obvious for one of skill in the art to modify the timing and dosage amounts reported in DiMartino to obtain the presently claimed methods (Office Action, page 5). Applicants respectfully traverse this rejection.

For rejection under 35 U.S.C. §103, there must be some suggestion or motivation to modify the cited reference to obtain the claimed invention. *See* MPEP §2143. The mere fact that a cited reference can be modified does not render the claims obvious unless the prior art suggests the desirability of the modification. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1990); MPEP §2143.01. Further, the cited reference must teach or suggest all of the claim limitations. MPEP §2142. The Office may not disregard express claim limitations or distill down to the "gist" of the invention. *See W.L. Gore &*

Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 1548 (Fed. Cir. 1983). Additionally, the Office must consider the unexpected results of the claimed invention as evidence of nonobviousness. *In re Dillon*, 919 F.2d 688, 692-693 (Fed. Cir. 1990); MPEP §2144.08(II)(B).

Applicants note that claims 1-29 have been cancelled herein without prejudice or disclaimer (see above). In addition, claims 30 and 47 currently read:

> 30. A method of treating diffuse large B-cell lymphoma in a subject, said method comprising the step of *orally administering* to the subject a total daily dose of *up to about 600 mg* of a pharmaceutical composition comprising suberoylanilide hydroxamic acid (SAHA) represented by the structure:  or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or diluent, wherein administration of SAHA is effective to treat diffuse large B-cell lymphoma in said subject. (Emphasis added)
>
> 47. A method of treating diffuse large B-cell lymphoma in a subject, said method comprising the step of *orally administering* to the subject a total daily dose of *up to about 800 mg* of a pharmaceutical composition comprising suberoylanilide hydroxamic acid (SAHA) represented by the structure:  or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or diluent, wherein the amount of SAHA is effective to treat diffuse large B-cell lymphoma in said subject. (Emphasis added).

The remaining claims ultimately depend from claims 30 or 47. Thus, all of the current claims encompass methods of treatment by orally administering to the subject a total daily dose of up to about 600 mg, or up to about 800 mg, of a pharmaceutical composition comprising suberoylanilide hydroxamic acid (SAHA).

In contrast to the instant claims, DiMartino fails to report any specific dosages or dosage schedules for oral administration of SAHA. Instead, DiMartino reports dosages only for *intravenous administration*, and only for HDAC inhibitors *depsipeptide*, *phenylbutyrate*, and *arginine butyrate* (see, *e.g.*, DiMartino, column 22, lines 10-30). It

is well known that depsipeptide, phenylbutyrate, and arginine butyrate are structurally disparate from SAHA. It is further known that intravenous and oral delivery can require widely differing dosages. Yet, the Examiner has provided no indication of how artisans could use DiMartino's intravenous dosages for structurally unrelated drugs to derive the specifically claimed oral dosages and schedules for SAHA. DiMartino fails to teach or suggest these claim elements, and no suggestion or motivation has been provided to modify DiMartino to obtain the instant claims. *See* MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990).

Moreover, the claimed methods of oral administration produce *unexpected half-life* for SAHA given the available knowledge in the art. *See* MPEP §716.02(a). Applicants show that oral administration of SAHA results in significantly longer half-life for the drug as compared to intravenous administration (see, *e.g.*, page 79, lines 9-11; Tables 2 and 3; and Figure 10 of the instant application). Oral SAHA produces a two- to three-fold increase in half-life as compared to intravenous delivery (see, *e.g.*, page 69, lines 14-24; page 70, Tables 2 and 3; and Figures 10 and 11 of the instant application; and Kelly *et al.*, 2005, *J. Clin. Oncol.* 23:3923-3931; Exhibit 4, page 3929, right column). The increased half-life for oral SAHA produces sustained histone acetylation in patients (Exhibit 4, page 3930, left column). The half-life for oral SAHA is surprising in view of prior cancer drugs, many of which exhibit short half-life (*e.g.*, high levels extraction in the gut wall or liver) from oral dosage (see, *e.g.*, Schellens *et al.*, 2000, *Eur. J. Pharm. Sci.* 12:103-110; Exhibit 5, page 103, right column to page 104, left column).

Thus, even if DiMartino could be modified and applied against the current claims (which Applicants still contest), the claimed methods of oral administration show unexpected advantages which could not have been known from the cited publication. *See U.S. v. Adams*, 383 U.S. 39, 50-51 (1966); MPEP §2144.08(II)(B).

Applicants conclude that the cited reference fails to teach or suggest the claimed oral doses and dosing schedules; no suggestion or motivation has been provided to obtain the specifically claimed oral doses and dosing schedules; and oral SAHA shows surprising half-life duration. For at least these reasons, DiMartino cannot make obvious

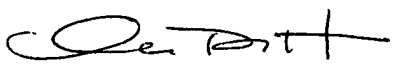
the current claims. From cancellations of claims 4-6, the rejections over DiMartino combined with WO 98/55449 and WO 95/31977 are made moot. Reconsideration is respectfully requested.

CONCLUSION

A favorable action on the merits is respectfully requested. If any discussion of this Amendment would be deemed helpful, the Examiner is encouraged to contact the undersigned at the telephone number provided below. Applicants believe no further fee is due at this time; however, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. **50-0311**, Reference No. **24852-501 CIP5**, Customer No. **35437**.

Date: January 11, 2006

Respectfully submitted,



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